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CLINICAL STUDIES

ST Segment Shift in Unstable Angina: Pathophysiology and Association With Coronary Anatomy and Hospital Outcome

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The significance of ST segment shift with respect to coronary anatomy and hospital outcome was evaluated in 135 patients with unstable angina. ST shift was evident in 44% of patients on admission electrocardiogram (ECG) and in 66% on Holter monitor ECG. During hospitalization, 7% of patients had myocardial infarction, 4% died and 34% had urgent coronary revascularization. By comparing patients with and without ST shift on admission ECG, an unfavorable outcome was found in 55% versus 25% ($p < 0.005$), multivessel disease in 77% versus 63% ($p < 0.05$) and left main coronary artery stenosis in 22% versus 7% ($p < 0.025$). When patients with and without ST shift on Holter monitor ECG were compared, an unfavorable outcome was found in 48% versus 20% ($p < 0.005$), multivessel disease in 76% versus 54% ($p < 0.01$) and left main coronary stenosis in 18% versus 4% ($p < 0.05$). The duration of ST shift was also greater in patients with 1) unfavorable outcome (129 ± 136 versus 52 ± 111 min, $p < 0.01$); 2) multivessel disease (98 ± 129 versus 36 ± 90 min, $p < 0.01$); and 3) left main stenosis (150 ± 147 versus 67 ± 114 min, $p < 0.01$).

A total of 593 episodes of ST shift were recorded by Holter monitor and only 8% were symptomatic; when compared with asymptomatic episodes, they were of longer duration (42 ± 50 versus 16 ± 27 min, $p < 0.01$) and had greater magnitude of ST shift (2.0 ± 1.3 versus 1.3 ± 0.5 mm, $p < 0.01$). Continuous blood pressure and heart rate recording in 446 episodes showed an increase in rate-pressure product at 20 and 10 min ($9.4 \pm 2.7 \times 10^3$, $p < 0.01$) before onset of ST shift as well as at the time of ST shift ($9.3 \pm 2.8 \times 10^3$, $p < 0.01$) as compared with the 2 h baseline value ($9.0 \pm 2.3 \times 10^3$).

Thus: 1) noninvasive tests can stratify patients with unstable angina into prognostic subsets with respect to hospital outcome and coronary anatomy; 2) episodes of ST shift associated with symptoms have a greater magnitude of ST shift and are of longer duration; and 3) myocardial ischemia, as demonstrated by onset of ST shift, may be mediated in part by increased myocardial oxygen demand as defined by an increase in rate-pressure product.

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Holter electrocardiographic (ECG) monitoring reveals frequent asymptomatic episodes of ST segment shift in patients with stable angina (1–8). Given our current understanding of the pathophysiology of unstable angina (9–14), coupled with the advanced symptoms and significant cardiac event rate in patients with this syndrome (15–18), it is not surprising that asymptomatic ST segment shift appears as a frequent feature of such patients (19–22). Although the outcome of unstable angina bears an important relation to coronary angiographic severity and complexity of disease (23,24), it is not feasible to catheterize all such patients, especially with limited health care resources. Thus a noninvasive technique that, applied early in the course of unstable angina, could identify those patients at increased risk would be helpful in assessing the need for angiographic studies.

Recent studies (21,22) suggest that the presence of silent ST segment shift in patients with unstable angina is associated with an unfavorable 1 and 6 month prognosis. Because such patients frequently require rapid decision-making during their current admission, it is important to know whether assessment of ST shift on an early Holter monitor ECG or admission ECG is of value in predicting unfavorable hospital outcome as well as angiographic severity of coronary artery disease. We therefore undertook the current prospective study to test the hypothesis that the presence of ST abnormality on admission ECG and the presence and duration of

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ST segment shift detected during 24 h Holter monitoring early in the course of unstable angina predict angiographic severity of coronary artery disease and hospital outcome in a consecutive group of patients. We also assessed changes in heart rate and blood pressure before and during the time of onset of ST shift to gain insight into the pathophysiology of myocardial ischemia in our patients.

Methods

Study patients. Over a consecutive period of 28 months, 196 patients with unstable angina were enrolled in the study. Unstable angina was defined as rapid acceleration of a previously established anginal syndrome to include rest pain or prolonged ischemic chest pain of >20 min duration without evidence of acute myocardial infarction, as defined by typical evolutionary changes on the ECG in association with serum cardiac enzyme elevation (evidence of enzymatic rise ≥2 × upper normal limits). Individuals were enrolled in the study if they were seen within 24 h of the last episode of ischemic chest pain at rest. They were excluded if they were >75 years of age or had a debilitating illness, left bundle branch block or previous aortocoronary bypass surgery. Of the 196 patients, 24 subsequently had enzymatic evidence that the presenting event was due to myocardial infarction and were, therefore, excluded. All patients gave informed consent and the protocol was conducted in a manner approved by a University of Toronto Ethics Review Committee. On the basis of the aforementioned criteria, the patients we enrolled represented 37% of all patients admitted to our coronary care unit for management of unstable angina. All patients were followed up by one of five cardiologists at St. Michael's Hospital, a tertiary care institution, whose approach to management of unstable angina was standardized.

For the purpose of this study, we examined all available ECG information from the time of qualifying chest pain to coronary care unit admission and selected the tracing with the most pronounced ST shift as the admission ECG. The standard protocol was to begin therapy with topical nitrates and calcium channel antagonists. Beta blockers were continued if the patient had been taking them before admission or added if the patient was unresponsive to the aforementioned therapy.

ST segment monitoring. Twenty-four hour ST segment monitoring was begun 6.5 ± 5.9 h after the qualifying episode of chest pain: the results were unavailable to the attending cardiologists. We used a two channel (leads V_5 and V_1) on-line computer-based digital Holter system (Medicomp, Epicardia HC) with a frequency response of 0.05 to 100 Hz in accordance with American Heart Association standards (25). We have previously validated this Holter system by comparison with the Marquette CASE exercise computer system using measurements of maximal ST shift at rest, during maximal exercise and immediately after exercise in 21 patients with coronary artery disease (r = 0.92, 0.87 and 0.94, respectively). Thirty-seven patients did not undergo Holter monitoring for technical reasons, and were excluded from subsequent analysis. Clinical outcome and coronary angiographic findings in these patients were not different from those in the rest of the group.

Of the remaining 135 patients who constituted the study group (93 male and 42 female, mean age 57 ± 10 years), all had 24 h of ECG recording on one channel and ≥16 h on the other. However, the majority of patients (86%) had 24 h of recording on both channels. An episode of ischemic ST shift from baseline was considered to be present if ≥1 mm (1 mm = 0.1 mV) ST elevation or horizontal or downsloping ST depression 80 ms from the J point was present for ≥60 s. For consideration as inclusion criteria, episodes of ST shift had to be separated from each other by ≥10 min.

Patients and attending nurses kept a careful diary of symptoms and they activated ST segment recording by pushing a button if chest discomfort was present. Silent ischemia was defined as occurrence of ischemic ST shift in the absence of symptoms.

Heart rate and blood pressure monitoring. On admission to the coronary care unit, an intraarterial line was inserted for continuous monitoring of blood pressure. Heart rate and blood pressure changes were recorded at 1 min intervals and were printed out in 2 h trend records throughout the first 24 h of admission. After excluding any hemodynamic perturbations occurring during ST shift, mean values for heart rate and blood pressure were determined during the 2 h period surrounding each episode of ST shift to serve as a baseline. The rate-pressure product was calculated at the onset and at 20 and 10 min before the onset of ST segment shift, and the values were compared with the baseline rate-pressure product.

Angiography. Selective coronary angiography was performed 4.2 ± 2.6 days after admission. The severity of coronary artery stenosis was assessed in multiple views by three experienced independent observers who were unaware of the results of Holter ECG monitoring. A significant stenosis was considered present if there was ≥50% narrowing of the lumen in the left anterior descending artery or its diagonal branch, the left circumflex artery or its obtuse marginal branches or the right coronary artery.

Unfavorable outcome. Unfavorable hospital outcome was defined as myocardial infarction, death or need for urgent aortocoronary bypass or percutaneous transluminal coronary angioplasty because of recurrent prolonged symptoms at rest refractory to maximal medical therapy.

Data analysis. Results are presented as mean values ± SD. To address our study hypothesis, we initially related total duration of ST shift to the findings of unfavorable hospital outcome, multivessel disease or left main coronary stenosis by analysis of variance. Because of recent reports (21,22), and after prospective collection of data was com-

pleted, we also classified our patients into three groups with respect to duration of ST shift: Group I (no ST shift), Group II (1 to 59 min duration of ST shift) and Group III (≥60 min of ST shift per 24 h of Holter monitoring). Because the distribution of ST shift duration was non-Gaussian, we performed log transformation for the purposes of statistical analysis. Comparison between groups with respect to baseline clinical characteristics was done by analysis of variance in the case of continuous variables and by chi-square analysis in the case of discrete variables. Odds ratio and 95% confidence intervals for unfavorable outcome were calculated in patients with ST shift on Holter monitoring. The best predictors of hospital outcome were determined by multiple regression analysis taking into account the clinical and laboratory variables of age, gender, history of hypertension, diabetes, previous myocardial infarction, smoking, number of episodes and duration of ischemic pain during the first 24 h of admission, number of episodes and duration of all ST shift, number of episodes and duration of silent ischemia, presence or absence of ST shift on admission ECG and number of vessels with ≥50% stenosis.

Differences between symptomatic and asymptomatic episodes as well as differences between the episodes with ST elevation and ST depression were compared with respect to duration and magnitude of ST shift with use of Student's unpaired *t* test. Differences in rate-pressure product in relation to 2 h baseline measurement were compared with use of two-way analysis of variance and Dunnett's test. The sensitivity of admission ECG and Holter monitor ECG with respect to unfavorable outcome was compared with use of McNemar's test.

Results

The clinical and angiographic characteristics of our study group as well as the details of antianginal therapy during the first 24 h of the hemodynamic and Holter monitoring are shown in Table 1. During hospitalization, 10 patients (7%) had nonfatal myocardial infarction and 6 patients (4%) died (3 in the peri-operative period). Six patients (4%) underwent urgent coronary angioplasty and 40 (30%) underwent urgent aortocoronary bypass operations. Nonurgent coronary angioplasty and bypass procedures were performed in an additional 19 patients (14%) and were not considered as an unfavorable outcome.

Admission electrocardiogram. Of the 135 patients, 34 (25%) had ST depression, 21 (16%) had ST elevation and 5 (4%) had both ST depression and ST elevation on the admission ECG. In comparison with patients who had isoelectric ST segments on the admission ECG, patients with ST depression on admission had a longer duration of ST shift on Holter monitoring (121 ± 145 versus 40 ± 78 min, $p < 0.01$) as did patients with ST elevation on admission (134 ± 147 versus 40 ± 78 min, $p < 0.01$).

Table 1. Clinical and Angiographic Characteristics of 135 Patients With Unstable Angina

Age (yr)	57 ± 10
Gender (male %)	69
Diabetes (%)	9
Smokers (%)	35
Hypertension (%)	37
Previous MI (%)	39
Previous angina (%)	67
Medications	
IV nitroglycerin (%)	28
All nitrates (%)	80
Beta-blockers (%)	46
Calcium antagonists (%)	74
Aspirin (%)	12
Coronary angiography	
0 Vessel disease (%)	15.5
1 Vessel disease (%)	15.5
2 Vessel disease (%)	18
3 Vessel disease (%)	51
Left main stenosis (%)	13

IV = intravenous; MI = myocardial infarction.

Holter ECG monitoring. Of the 135 patients, 89 (66%) had ST shift on Holter monitoring; 55 (62%) had ST depression, 18 (20%) had ST elevation and 16 (18%) had both ST elevation and depression. In the 89 patients with ST shift, the mean baseline ST level during 24 h of Holter monitoring was −0.5 ± 0.8 mm in lead V_5 and 0.2 ± 0.7 mm in lead V_1. The mean duration of ST shift in the 24 h period after admission was 119 ± 133 min (range 1 to 577). There were a total of 593 episodes of ST shift with an average of 6.7 episodes/patient (range 1 to 23). The duration of each episode averaged 18 ± 30 min (range 1 to 230).

Among 135 patients, 62 were receiving a beta-adrenergic blocker while undergoing Holter monitoring. The duration of ST shift in these patients was similar to that of patients not receiving a beta-blocker (91 ± 133 versus 68 ± 110 min, p = NS).

When patients were classified according to duration of ST shift, 46 had no ST shift (Group I), 44 had ST shift of 1 to 59 min duration (Group II) and 45 patients had ST shift of ≥60 min duration (Group III).

Asymptomatic versus symptomatic ST shift. Of 89 patients with ST shift on Holter ECG monitor, the majority (68%) had silent ischemia exclusively as compared with 6% of patients in whom the ST shift was always symptomatic. The remaining 26% of the patients had both symptomatic and asymptomatic ST shift.

Among 593 episodes of ST shift on Holter ECG monitoring 547 (92%) were asymptomatic and 46 (8%) were symptomatic. The duration of symptomatic episodes was significantly longer than that of asymptomatic episodes (41 ± 49 versus 16 ± 27 min, $p < 0.01$). The difference in magnitude of ST shift between the symptomatic and asymptomatic

Table 2. Relation Between Rate-Pressure Product and ST Shift on Holter Monitoring

Type of Episode	Time of Measurement	2 h Baseline	Before ST Shift		Onset of ST Shift
			20 min	10 min	
All episodes (n = 446)					
	HR	70 ± 13	70 ± 14	72 ± 15	71 ± 16
	SBP	128 ± 19	128 ± 23	130 ± 22	130 ± 22
	RPP	9.0 ± 2.3	9.1 ± 2.6	9.4 ± 2.7*	9.3 ± 2.8*
Asymptomatic (n = 412)					
	HR	70 ± 14	70 ± 14	72 ± 15	71 ± 16
	SBP	128 ± 19	129 ± 22	131 ± 22	130 ± 22
	RPP	9.0 ± 2.3	9.2 ± 2.6	9.4 ± 2.7*	9.2 ± 2.8*
Symptomatic (n = 34)					
	HR	67 ± 9	68 ± 11	71 ± 11	72 ± 12
	SBP	128 ± 19	124 ± 20	127 ± 17	134 ± 23
	RPP	8.9 ± 2.0	8.6 ± 2.2	9.2 ± 2.0	9.9 ± 2.6†
ST elevation (n = 140)					
	HR	70 ± 15	71 ± 13	72 ± 16	71 ± 17
	SBP	125 ± 19	125 ± 20	126 ± 20	125 ± 22
	RPP	8.7 ± 2.1	8.9 ± 2.4	9.1 ± 2.6	9.0 ± 2.7
ST depression (n = 306)					
	HR	70 ± 13	70 ± 13	72 ± 14	71 ± 16
	SBP	130 ± 19	130 ± 23	132 ± 22	132 ± 22
	RPP	9.1 ± 2.4	9.2 ± 2.7	9.5 ± 2.7*	9.4 ± 2.8*

*$p < 0.01$; †$p < 0.05$. HR = heart rate (beats/min); RPP = rate-pressure product (HR × BP × 10^3); SBP = systolic blood pressure (mm Hg).

episodes was detected in episodes with ST depression (−1.8 ± 0.8 versus −1.3 ± 0.4 mm, $p < 0.01$) as well as ST elevation (2.5 ± 1.8 versus 1.4 ± 0.7 mm, $p < 0.01$). When asymptomatic episodes in patients with both symptomatic and asymptomatic episodes were compared with asymptomatic episodes in patients who had only asymptomatic episodes, no difference was found with respect to duration (14 ± 17 versus 16 ± 29 min, p = NS) or magnitude of ST shift (1.4 ± 0.6 versus 1.3 ± 0.4 mm, p = NS). Both symptomatic and asymptomatic episodes were predominantly associated with ST depression, (72% and 67%, respectively, p = NS).

ST depression versus ST elevation. Of 593 episodes of ST shift, in 405 (68%) the ST segment was depressed and in 188 (32%) it was elevated. Episodes with ST elevation were similar in duration to those with ST depression (17 ± 30 versus 18 ± 30 min, p = NS); however, they were associated with greater magnitude of ST shift when compared with episodes with ST depression (1.5 ± 0.9 versus 1.3 ± 0.5 mm, $p < 0.01$).

Patients exhibiting either ST depression or ST elevation, or both, on Holter monitoring were not different with respect to frequency of multivessel disease (71%, 72% and 94%, respectively), left main stenosis (16%, 11% and 31%) or unfavorable outcome (46%, 50% and 62%). The occurrence of ST shift on the Holter ECG monitor was independent of previous myocardial infarction; 41% of patients with ST shift had previous myocardial infarction as compared with 35% of patients without ST shift (p = NS). There was also no difference in frequency of previous myocardial infarction between patients with ST elevation and those with ST depression on Holter monitoring.

Heart rate and blood pressure monitoring (Table 2). In 446 episodes of ST shift, heart rate, blood pressure and rate-pressure product records were available for analysis. These were recorded during a 2 h baseline period, at 20 and 10 min before the onset of ST shift and at the onset of ST shift. When all episodes were considered, there was a slight but significant rise in rate-pressure product 10 min before the onset of ST shift as compared with baseline. Rate-pressure product at the time of onset of ST shift was also higher than at baseline but showed no further increase when compared with the value 10 min before the onset of ST shift. When episodes were classified according to the presence or absence of symptoms, or the presence of ST elevation or ST depression, a similar trend of increasing rate-pressure product before the onset of ST shift was noted.

To evaluate the maximal changes in rate-pressure product during each episode of ST shift, we compared the 2 h baseline value with that recorded either at 10 min before the ST shift or at its onset (Fig. 1). The increase in rate-pressure product was >10% in >40% of episodes and >20% in >17% of episodes. The mean change in rate-pressure product was an increase of 10 ± 15% and the median change was an increase of 7%. The rise in rate-pressure product during symptomatic episodes was substantially greater than that

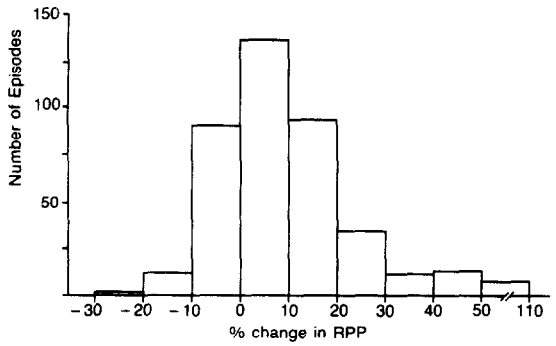

Figure 1. Distribution of 446 episodes with ST segment shift according to maximal percent change in rate-pressure product (RPP) (at either the onset of ST shift or 10 min before its onset) compared with the value at 2 h baseline.

seen during asymptomatic episodes (17 ± 20% versus 10 ± 15%, $p < 0.05$); the majority of this change occurred at the time of onset of ST shift. To partition the influence of symptoms on rate-pressure product changes during symptomatic ST shift, we also evaluated the changes during episodes of chest pain not associated with ST shift; we found no significant increase in rate-pressure product from baseline.

Coronary angiography. Multivessel disease was present in 93 patients (69%) and left main stenosis was found in 18 (13%) (Table 1). More patients with ST depression on the admission ECG had multivessel disease then did those with no ST shift (77% versus 63%, $p < 0.05$); similarly, left main stenosis was more frequent when ST depression was present on admission ECG (28% versus 7%, $p < 0.025$). Patients with ST elevation on the admission ECG had the same frequency of multivessel disease and left main stenosis as did those with no ST shift (69% versus 63% and 15% versus 7%, respectively, p = NS).

Patients with multivessel disease, as compared with patients without multivessel disease, had a longer duration of ST shift on the Holter monitor (98 ± 129 versus 36 ± 90 min, $p < 0.01$), more frequent episodes of ST shift (7.3 ± 5.2 versus 4.5 ± 3.4 episodes, $p < 0.05$) and a longer duration of ST shift per episode (18 ± 12 versus 11 ± 11 min, $p < 0.05$). The duration of ST shift was also longer in those patients with versus those without left main stenosis (150 ± 147 versus 67 ± 114 min, $p < 0.01$).

In comparison with patients without ST shift (Group I), the 89 patients with ST shift on Holter monitoring (Groups II and III) were found to have a higher frequency of multivessel disease (76% versus 54%, $p < 0.01$) and left main stenosis (18% versus 4%, $p < 0.05$). Patients in Group III (ST shift ≥60 min) had a significantly greater incidence of multivessel disease (89%) and left main stenosis (27%) as compared with patients in Group I (54% and 4%, respectively, $p < 0.025$) or Group II (ST shift <60 min) (64% and 9%, respectively, $p < 0.05$). No intergroup differences were evident with respect to baseline clinical characteristics (Table 1) or in time to the start of Holter monitoring. Before admission, more patients in Group III (76%) were taking nitrates than were those in Group I (48%, $p < 0.025$) or Group II (52%, $p < 0.05$) and more in Group III (76%) were taking a calcium antagonist than were those in Group II (43%, $p < 0.005$). During Holter monitoring, more patients in Group III (89%) were taking a calcium antagonist than were those in Group I (65%, $p < 0.025$) or Group II (68%, $p < 0.05$).

Unfavorable hospital outcome. Of the 135 patients, 52 had an unfavorable outcome that occurred at a mean of 4.5 ± 3.2 days. Compared with the other 83 patients, those with an unfavorable outcome were taking more antianginal medications (2.6 ± 0.5 versus 2.3 ± 0.8 drugs/person, $p < 0.01$). These medications consisted of nitrates in all patients, a calcium antagonist in 98% and a beta-blocker in 65% of patients.

An unfavorable outcome was more frequent in patients with ST depression (56%) or ST elevation (54%) than in patients with no ST shift on the admission ECG, (25%, $p < 0.01$ and $p < 0.05$, respectively). Patients with an unfavorable outcome had a longer duration of ST shift on the Holter monitor (129 ± 136 versus 52 ± 111, $p < 0.01$), more frequent episodes of ST shift (7.0 ± 5.9 versus 2.9 ± 3.9, $p < 0.01$), and longer duration of ST shift per episode (16 ± 14 versus 7 ± 11 min, $p < 0.01$). Patients with ST shift on the Holter monitor had a more frequent unfavorable outcome when compared with those with no ST shift (48% versus 20%, $p < 0.005$; odds ratio 3.79 with 95% confidence interval from 1.62 to 8.89). Patients in Group III (ST shift ≥60 min) had an increased incidence of unfavorable outcome (67%) as compared with that in patients in Group I (no ST shift) (20%, $p < 0.025$; odds ratio 8.83 with 95% confidence interval from 5.39 to 12.88) or Group II (ST shift <60 min) (30%, $p < 0.05$; odds ratio 4.52 with 95% confidence interval from 1.76 to 11.6).

Recognizing that the basis for recommending coronary revascularization has a subjective component, we also analyzed the results of Holter monitoring using only "hard" end points, that is, nonfatal myocardial infarction and death. Patients with these end points had a significantly longer duration of ST shift than did patients without these end points (147 ± 137 versus 69 ± 117 min, $p < 0.05$). Patients in Group III (ST shift ≥60 min) had more frequent nonfatal myocardial infarction and death than did patients in Group I (no ST shift) (20% versus 4%, $p < 0.05$). No difference was found between Groups III and II (ST shift <60 min) (20% versus 11%, p = NS) or Groups II and I (11% versus 4%, p = NS).

Patients with an unfavorable outcome had a slightly greater ST shift when compared with patients who did not have an unfavorable outcome (1.5 ± 0.8 versus 1.3 ± 0.4 mm, $p < 0.01$).

There was a good correlation between the duration of ST

shift and the frequency of episodes of ST shift in our study ($r = 0.90$). There was no difference in positive predictive value of ≥5 episodes of ST shift versus duration of ≥60 min with respect to unfavorable outcome (63% versus 67%), multivessel disease (85% versus 89%) and left main stenosis (23% versus 26%).

Seventy-four of 135 patients had recurrent chest pain in the first 24 h after admission. ST shift on Holter monitoring occurred in 69% of these and in 62% of patients without recurrent chest pain (p = NS). Sixty-five percent of patients with recurrent chest pain that was not associated with ST shift had a normal admission ECG, and this group had a similar frequency of unfavorable outcome as patients without recurrent chest pain. However, more patients with recurrent chest pain associated with any ST shift during Holter monitoring had an unfavorable outcome than did patients with an ST shift alone (69% versus 41%, $p < 0.025$).

We used a multiple regression model to define the best predictors of unfavorable outcome. Of 14 clinical and laboratory variables, coronary anatomy on angiography was found to be the best predictor ($F = 44.3$, $p < 0.0001$). When the results of angiography were removed from the model, the duration of ST shift on Holter recording was found to be the best predictor of unfavorable outcome ($F = 18.1$, $p < 0.0001$). The third best predictor of unfavorable outcome was age ($F = 10.43$, $p < 0.001$).

The admission ECG was less sensitive than was Holter ECG monitoring in identifying patients with unfavorable outcome (63% versus 83%, respectively, $p < 0.005$). Among the 52 patients with an unfavorable hospital outcome, 33 were identified by the presence of ST shift on the admission ECG; the results of Holter monitoring in these patients did not further increase the sensitivity. By contrast, in 75 patients without ST shift on the admission ECG, Holter monitoring identified an additional 15 patients with an unfavorable outcome. Hence, only 4 of 52 patients with an unfavorable outcome did not have ST shift on either the admission ECG or Holter ECG monitoring.

Among the 93 patients with multivessel disease, the 68 patients with ST shift on Holter monitoring more frequently had an unfavorable outcome as compared with the 25 patients with no ST shift (62% versus 28%, $p < 0.01$). Thus, the presence of ST shift on Holter monitoring was helpful in identifying patients with an unfavorable outcome both before and after the results of coronary angiography were available.

Discussion

Our study provides new and comprehensive information relating the analysis of ST shift on the admission ECG and 24 h Holter ECG monitoring to angiographic characteristics and hospital outcome in patients with unstable angina. We also present new data on analysis of hemodynamic changes in association with episodes of ST shift in these patients.

Admission ECG. The significance of the admission ECG with respect to presence or absence of ST shift in patients with unstable angina has not been previously evaluated. Earlier studies assessing the treatment of unstable angina (17) and the value of Holter monitoring (21,22) have used ST shift on the admission ECG as part of study entry criteria. This procedure creates a selection bias and precludes the capacity to assess the prognostic value of the admission ECG. Despite a careful search for ST shift, we found that only 44% of the 135 patients had ST segment depression or elevation on the admission ECG and these patients more frequently had an unfavorable outcome than did those who had isoelectric ST segments. However, because attending cardiologists were aware of the results of the admission ECG, their patient management and, in particular, the decision to recommend revascularization may have been influenced by this information.

Patients with ST shift on the admission ECG also had a longer duration of ST shift on Holter monitoring when compared with patients with normal ST segments on admission. In fact, the presence of ST shift on the admission ECG had a positive predictive value of 80% for finding ST shift on Holter monitoring. Despite the prognostic value of the admission ECG, among patients with a normal admission ECG, 25% had an unfavorable outcome, 63% had multivessel disease and 7% had left main stenosis.

Holter ECG monitoring. Previous studies (21,22) have shown that an arbitrary classification of silent ischemia ≥60 min in duration is associated with an unfavorable 1 and 6 month prognosis. In addition to demonstrating that the presence of any ST shift, silent or symptomatic, predicts unfavorable hospital outcome, our study provides a prospective validation of the use of ST shift of ≥60 min duration as a criterion for unfavorable outcome.

Our finding of more frequent multivessel disease and left main stenosis in patients with ≥60 min ST shift is similar to that of Nademanee et al. (22) but different from the data of Gottlieb et al. (21). The smaller number of patients and incomplete angiographic data in the latter study may account for the differences observed.

The significance of ST elevation versus ST depression in patients with unstable angina has not been previously addressed. We found no differences between these variables in duration of ST shift or association with occurrence of multivessel disease, left main stenosis and unfavorable outcome. Episodes of ST elevation, however, were less frequent than episodes of ST depression and were associated with a greater magnitude of ST shift. The reasons for occurrence of ST elevation versus ST depression remain unclear.

The relative frequency of asymptomatic ST shift was similar to that found in previous studies (21,22); however,

previous studies did not compare symptomatic and asymptomatic episodes. We found that symptomatic episodes were of longer duration and had a greater magnitude of ST shift than did asymptomatic episodes. This new and important finding suggests that episodes of symptomatic ST shift on Holter monitoring are associated with a greater extent of myocardial ischemia as compared with episodes of silent ischemia. However, symptomatic episodes constituted a small minority (8%) of all episodes of ST shift. Importantly, it was the total duration of ST shift (symptomatic and asymptomatic) that was associated with multivessel disease, left main stenosis or unfavorable hospital outcome. In fact, duration of ST shift on Holter ECG monitoring was the best noninvasive predictor of unfavorable outcome when all the other conventional factors were taken into account.

Rate-pressure product and ST shift. Assessment of hemodynamic changes in relation to onset of myocardial ischemia has been addressed in two previous studies (26,27). Maseri et al. (27) studied 22 patients with vasospastic angina at rest and found no increase in heart rate or blood pressure preceding the episodes of ST shift. Cannom et al. (26) studied patients with unstable angina and found that some had an increase in rate-pressure product in association with anginal episodes. Because Holter monitoring was not performed and hemodynamic monitoring was intermittent, they did not assess the exact sequence of hemodynamic changes preceding the onset of myocardial ischemia. A strength of our study is that we continuously monitored heart rate and blood pressure throughout the period of Holter monitoring and, therefore, were able to study changes in rate-pressure product both before and at the time of onset of ST shift. We found a slight, but significant increase in rate-pressure product preceding the onset of ST shift and propose that small increases in myocardial oxygen demand may provoke myocardial ischemia in at least some patients with unstable angina and severe impairment of coronary flow. Given that a substantial number of episodes of ST shift had either no change or a decline in rate-pressure product in association with ST shift (Fig. 1), a primary reduction in myocardial perfusion was likely also an important factor. Because we did not measure coronary blood flow, the relative contributions of myocardial oxygen delivery and oxygen demand as modulators of ischemia could not be directly evaluated.

Symptomatic versus asymptomatic episodes. Symptomatic episodes of ST shift were associated not only with a greater duration and magnitude of ST shift, as compared with asymptomatic episodes, but also with a greater increase in rate-pressure product at the time of onset of ST shift. It is possible that this increase was a result of sympathetic stimulation secondary to symptoms. However, our finding that a significant increase in rate-pressure product occurred in association with asymptomatic episodes but did not occur during episodes of chest pain without ST shift lends support to the potential pathogenetic role of an increase in myocardial oxygen demand in symptomatic patients with ST shift.

In summary, our data, drawn from a broad cross section of patients with unstable angina and normal or abnormal findings on the admission ECG, indicate that, although symptomatic ST shift is associated with a greater extent of myocardial ischemia, symptoms alone are an inadequate guide for management of patients with unstable angina. When both ischemic pain and ST shift are present, however, severe coronary artery disease and poor hospital outcome are more frequent. Monitoring of either the duration or the number of episodes of ST segment shift provides a better assessment of the total ischemic burden than does angina alone. The presence of ST shift should alert the physician to intensify medical therapy or to perform coronary angiography to identify those patients who have multivessel disease or left main stenosis who may be better served by revascularization. When health resources are limited, physicians should first identify those patients with ST shift on the admission ECG because they have an increased frequency of multivessel disease, left main stenosis and unfavorable hospital outcome. In patients without ST shift on admission, Holter monitoring will help to identify those with severe coronary artery disease and unfavorable hospital outcome. The results of Holter monitoring are of additional prognostic value in patients who are found to have multivessel disease.

Our findings indicate that in patients with unstable angina: 1) analysis of the ST segment on the admission ECG and Holter ECG monitoring can stratify patients with unstable angina into prognostic subsets with respect to unfavorable hospital outcome and coronary anatomy; 2) when episodes of ST shift are associated with symptoms, the shift is of greater magnitude and of longer duration; 3) myocardial ischemia, as demonstrated by the onset of ST shift, may be mediated in part by increased myocardial oxygen demand, as defined by an increase in rate-pressure product.

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